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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KERR, KATHLEEN M	

ART UNIT	PAPER NUMBER
1652	25

DATE MAILED: 04/28/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Offic Action Summary	Application No.	Applicant(s)	
	09/478,598	RAO ET AL.	
	Examiner	Art Unit	
	Kathleen M Kerr	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *54-58,60-65,67-72,75-80,82,83,97-105 and 119-124* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *54-58,60-65,67-72,75-80,82,83,97-105 and 119-124* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 February 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Application Status

1. In response to the previous Office action, a non-Final rejection (Paper No. 20, mailed on November 19, 2002), Applicants filed a response and amendment received on February 7, 2003 (Paper No. 24). said amendment cancelled Claims 59, 66, 73, 74, 81, 84-96, and 106-118, amended Claims 54, 57, 58, 60-63, 65, 67-69, 72, 75, 80, 82, 97, 99, and 105, and added new Claims 119-124. Thus, Claims 54-58, 60-65, 67-72, 75-80, 82, 83, 97-105, and 119-124 are pending in the instant Office action and will be examined herein.

Priority

2. As previously noted, the instant application is granted the benefit of priority for the U.S. non-Provisional Application No. 08/988,015 filed on December 10, 1997.

Drawings

3. In response to the previous Office action, Applicants filed formal drawings (Paper No. 23) on February 7, 2003. Said drawings have been approved by the Draftsmen and are, therefore, entered as formal drawings acceptable for publication upon the identification of allowable subject matter.

Sequence Compliance

4. By virtue of Applicant's amendment to the description of the drawings in the specification, the instant application now fully complies with the sequence rules.

Withdrawn - Objections to the Specification

5. Previous objection to the drawings for having inappropriate labels is withdrawn by virtue of Applicant's amendment to the drawings.

6. Previous objection to the specification for being confusing with respect to the sequence listing is withdrawn by virtue of Applicants' amendment to the specification to include all SEQ ID NOs mentioned in the listing.

7. Previous objection to the Abstract for not completely describing the disclosed subject matter is withdrawn by virtue of Applicants' amendment.

8. Previous objection to the specification for typographical errors is withdrawn by virtue of Applicants' amendment.

Withdrawn - Claim Objections

9. Previous objection to Claims 60, 62, and 117 for typographical errors is withdrawn by virtue of Applicants' amendment.

10. Previous objection to Claims 59, 74, and 99 under 37 C.F.R. § 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim is withdrawn by virtue of Applicants' amendment.

11. Previous objection to Claims 70, 115, and 116 under 37 C.F.R. § 1.75 as being substantial duplicates of Claims 58, 69, and 71, respectively, is withdrawn by virtue of Applicants' amendment.

Withdrawn - Claim Rejections - 35 U.S.C. § 112

12. Previous rejection of Claims 54-68, 117, and 118 under 35 U.S.C. § 112, second paragraph, as being indefinite for the phrase "whose conformation is unavailable" is withdrawn by virtue of Applicants' amendment.

13. Previous rejection of Claims 57 and 72 under 35 U.S.C. § 112, second paragraph, as being indefinite for the term "dimerizing proteins" is withdrawn by virtue of Applicant's amendment.

14. Previous rejection of Claims 65, 80, and 105 under 35 U.S.C. § 112, second paragraph, as being indefinite for the term "correctly folded variants" is withdrawn by virtue of Applicants' amendment.

15. Previous rejection of Claims 66, 67, 81, 82, 106, and 107 under 35 U.S.C. § 112, second paragraph, as being indefinite for the phrase "increased to represent 5% of the total amino acid content" is withdrawn by virtue of Applicant's amendment.

16. Previous rejection of Claims 57 and 72 under 35 U.S.C. § 112, first paragraph, new matter, is withdrawn by virtue of Applicant's amendment.

Withdrawn - Claim Rejections - 35 U.S.C. § 102

17. Previous rejection of Claims 54-57, 61-62, 64-65, and 117-118 under 35 U.S.C. § 102(b) as being anticipated by Berkner (USPN 5,288,629) is withdrawn by virtue of Applicants' amendment requiring that the alterations be at least to 10% of the entire protein; Berkner *et al.* teach a point mutation.

Withdrawn - Claim Rejections - 35 U.S.C. § 103

18. Previous rejection of Claims 54-62, 64-66, 68-77, 79-81, 83, 97-102, 104-106, 115-118 under 35 U.S.C. § 103(a) as being unpatentable over Dyer *et al.* in view of Goldberg is withdrawn by virtue of Applicants' amendment. All the independent claims now require an alteration of at least 10% amino acid content; this particular limitation is not explicitly taught in the art. The closest prior art is Dyer *et al.* who teach mutating 30 methionines into a 397 amino acid protein for a change in amino acid content of 7.6%.

19. Previous rejection of Claims 78 and 103 under 35 U.S.C. § 103(a) as being unpatentable over Dyer *et al.* in view of Goldberg and in view of Arnold *et al.* is withdrawn by virtue of Applicants' amendment. All the independent claims now require an alteration of at least 10% amino acid content; this particular limitation is not explicitly taught in the art.

NEW REJECTIONS

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

20. Claims 54-58, 60-65, 67-72, 75-80, 82, 83, 97-105, and 119-124 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In Claims 54, 58, 69, and 97 (the independent claims), the "said confirmation" item (either item c or d) is unclear as to whether or not it is a method step. Presently, the only real method steps is "introducing" although a confirming step is implied. Clarification is required. The Examiner suggests rewriting the independent claims to include method steps (a) introducing... and (b) confirming the confirmation and add the wherein clauses at the end of the claim (without lettering) for clarity of the steps required to practice the claimed method.

21. Claims 64 and 79 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 64 limits to specific methods of introduction of random mutations (see page 6 of the specification, and Claim 122). However, Claim 64 depends from Claim 62 which depends from Claim 61 drawn to making mutations at predetermined sites. This inconsistency is confusing. Clarification is required. The Examiner suggests changing the dependency of Claim 64 to depend from Claim 63.

Claim 79, drawn to specific methods of random mutagenesis, is confusing as it depends from Claim 69; appropriate and consistent dependency would be from Claim 78, drawn to random mutagenesis in general. Clarification is required.

22. Claims 64, 79, 103, and 123 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which

applicant regards as the invention. The instant claims are confusing based on their inconsistency with the specification. On page 6, random methods of mutagenesis are described as being mutagenic PCR or DNA shuffling; phage display methodology is described as a way of assessing the random mutants produced. Thus, it is unclear how phage display methodology is used for random mutagenesis in the absence of mutagenic PCR and/or DNA shuffling. Clarification is required. The Examiner suggests the following amendment for clarity

---wherein said amino acid changes are produced using mutagenic PCR or DNA shuffling, either optionally in combination with phage display methodology---.

23. Claim 67 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The antecedent basis of "said nutritionally essential amino acids" in Claim 58 is unclear. Clarification is required.

24. Claim 99 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "rather than" is unclear. Must the claimed method comprise only substitutions, or is substitution preferably, but deletions or additions also meet the limitations? Clarification is required.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

25. Claim 99 is rejected under 35 U.S.C. § 112, first paragraph, new matter, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The phrase "comprise substitutions rather than deletions or additions" does not have support in the specification as originally filed. Applicants must specifically cite (page and line number) support in the specification as originally filed or delete the new matter from the claim. Explanation or correction is required.

26. Claims 54-58, 60-65, 67-72, 75-80, 82, 83, 97-105, and 119-124 are rejected under 35 U.S.C. § 112, first paragraph, enablement, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The instant claims are drawn to methods of introducing multiple amino acid changes (at least 10% of the protein content) into a protein while not inducing conformational changes in said protein, wherein the conformation of said protein is confirmed by interacting the mutant with molecules.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by

weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

The instant specification describes a single example **related** to the pending claims wherein vegetative storage protein-β (VSPβ) from *Glycine max*, a 218 amino acid protein, is mutated to increase its methionine content by 18 methionines (VSPβ-met10); this represents a change in amino acid content of 8.25%, not at least 10% (the Examiner reiterates here that Dyer *et al.* teaches a change of 7.6% - see above withdrawal of art rejection). The VSPβ-met10 is then expressed and assayed for its ability to bind a monoclonal antibody specific for VSPβ; the mutant, just like the wild-type, is recognized by the antibody.

"Interacting molecules"

Firstly, the instant specification does not teach that the interaction of monoclonal antibodies is indicative of native conformation. In fact, as clearly known in the art, the interaction of any particular antibody with its antigen (protein) relies solely on the presence of an epitope. An assay with a monoclonal antibody merely tests for the conformation of the epitope, and NOT the conformation of the entire 218 amino acid protein. Thus, the binding of a monoclonal antibody is not necessarily predictive of a native (wild-type-like) conformation of a mutant protein; the only structural data that can "confirm" (as required by the claims) native

protein conformation is three-dimensional crystal structure data which is in no way described in the instant specification.

Similarly, interaction of homodimers (VSPβ-VSPβ) relies solely on the interface of the two individual proteins. Sides of mutant proteins that do not interact could have wholly different conformations from that of wild-type (native) protein while dimerization still occurs. An assay between a VSPβ mutant and VSPβ wild-type, which tests for heterodimer formation, merely tests for the conformation of the interface, and NOT the conformation of the entire 218 amino acid protein. Thus, the binding of a heterodimers is not necessarily predictive of a native (wild-type-like) conformation of a protein; the only structural data that can "confirm" (as required by the claims) native protein conformation is three-dimensional crystal structure data which is in no way described in the instant specification.

Additionally, interacting molecules (in claims that do not limit the term to antibodies and/or heterodimers) can be any molecule that interacts with a protein of interest (or VSP). On page 5 of the specification, examples are noted to include nucleotide sequences and carbohydrates while the art would also include such molecules as inhibitors and substrates. As noted above for antibody and heterodimer interaction, the interaction of any of these molecules assays only the recognition site between the mutant and the nucleotide sequence or substrate, for example. Such assays do not test for the entire conformation of the mutant protein.

Thus, it is clear that "interacting molecules" do NOT "confirm" the conformation of a mutant protein to be that of the native (wild-type) protein.

"At least 10%" alteration of amino acid content

The instant specification provides no working examples for producing a mutant VSP protein that maintains native conformation while having been altered in its amino acid composition by at least 10%. The example in the specification changes the content by 8.25%. Description of more extensive mutants is found (see Tables), but none are brought to fruition. It is wholly unpredictable whether or not the native conformation (or even a conformation recognized by the monoclonal antibody described) can be maintained with such extensive modification to the small protein sequence. On page 16 of the specification, it is noted that 51 out of 218 amino acid positions are postulated for mutation to hydrophobic residues and its "possible" that the VSP protein "might tolerate" all of said changes. The state of the prior art is extensive with numerous examples of alteration of amino acid content, but none to the extent of 10% of the amino acid composition while maintaining the native conformation.

Additionally, some of the instant claims are drawn to mutating your own "protein of interest". No direction as to the allowed changes for every known protein in the art is taught. No working examples, other than that of VSPβ, are taught. No antibodies or other protein-of-interest:interacting molecule pairs are taught. In the state of the art, it is highly foreseeable that many proteins cannot be subjected to this level of mutagenesis and maintain any sort of native conformation. The specification presents no guidance for discerning which proteins are suitable for the claimed methods or for discerning where in those suitable proteins mutagenesis would be most productive in the claimed methods.

Moreover, specifically for Claims 67 and 82, methods that include mutating to change at least 20% of the amino acid content are also not enabled for the reasons noted above.

Summary of Pending Issues

27. The following is a summary of the issues pending in the instant application that MUST be addressed in response to the instant Office action:

a) Claims 54-58, 60-65, 67-72, 75-80, 82, 83, 97-105, and 119-124 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the step of determining the confirmation as it pertains to a clear method step or not.
b) Claims 64 and 79 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the limits to specific methods of introduction of random mutations.
c) Claims 64, 79, 103, and 123 stand rejected under 35 U.S.C. § 112, second paragraph, as being inconsistent in the noted random methods of mutagenesis.
d) Claim 67 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the antecedent basis of "said nutritionally essential amino acids".
e) Claim 99 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the phrase "rather than".
f) Claim 99 stands rejected under 35 U.S.C. § 112, first paragraph, new matter.
g) Claims 54-58, 60-65, 67-72, 75-80, 82, 83, 97-105, and 119-124 stand rejected under 35 U.S.C. § 112, first paragraph, enablement.

Conclusion

28. No claims are allowed for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

The instant Office action is **NON-FINAL** based on the reiteration of the previously withdrawn enablement rejection, as it related to the interacting molecules, and to the newly set forth aspect of the enablement rejection relating to changing at least 10% of the amino acid content of either VSP or any protein of interest.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (703) 305-1229. The examiner can normally be reached on Monday through Friday, from 8:30am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

KMK
April 24, 2003